peak, it was not possible to obtain HRMS for this compound.

6d (65% yield). Oil. IR: 3310, 1755 cm^{-1}. MS: 317 (M^+, 13), 273 (M^+ - 44, 4.6), 201 (imine$^+$, 100). NMR: δ 7.4-6.3 (series of m, 7 H), 5.1 (s, 1 H), 4.2 (q, 1 H, J = 5.2 Hz), 3.7 (s, 3 H), 3.4 (s, 3 H), 1.3 (d, 3 H, J = 5.2 Hz). HRMS: calcd for $C_{17}H_{19}NO_5$ 317.1393, found 317.1271.

The TBDMS derivative of **6a** was prepared in 89-95% yield by silylation[17] and purified (5:1 hexane-ethyl acetate). MP: 100-101 °C. IR: 1750 cm^{-1}. MS: 467 (M^+, 4.5), 436 (M^+ - 31, 2.8), 237 (imine$^+$, 94.4), 236 (imine$^+$ - 1, 100). NMR: δ 7.4-7.2 (m, 7 H), 6.8 (m, 3 H), 6.2 (dd, 1 H, J = 7.8 Hz, J = 16.0 Hz), 4.7 (dd, 1 H, J = 0.9 Hz, J = 7.8 Hz), 4.1 (q, 1 H, J = 6.3 Hz), 3.7 (s, 3 H), 3.6 (s, 3 H), 1.3 (d, 3 H, J = 6.3 Hz), 0.7 (s, 9 H), 0.06 (s, 6 H). Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a CH_2Cl_2-hexane solution.[18]

Conversion of 5a to 7a. (i) A 0.353-g (1-mmol) sample of **5a** was dissolved in about 10 mL of dry CH_2Cl_2, and 0.23 mL (2 mmol) of 2,6-lutidine and 0.32 mL (1.5 mmol) of TBDMS-triflate were added. The clear homogeneous solution was heated under reflux for 3 h under N_2. The reaction mixture was allowed to warm to room temperature, and the solvent was removed under reduced pressure. The resulting yellow oil was chromatographed (5:1 hexane-ethyl acetate) to furnish the enol silyl ether in 95% yield as a yellow semisolid. IR: 1745 cm^{-1}. MS: 465 (M^+, 6.3), 434 (M^+ - 31, 3.2), 408 (M^+ - 57, 40.5), 237 (imine$^+$, 89), 236 (imine$^+$ - 1, 100). NMR: δ 7.3-7.1 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, J = 8.2 Hz, J = 16.0 Hz), 4.6 (d, 1 H, J = 1.9 Hz), 4.3 (d, 1 H, J = 1.9 Hz), 4.0 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 3 H), 0.8 (s, 9 H), 0.0 to -0.15.

(ii) Br_2 (0.33 g, 2.1 mmol) in 10 mL of dry CH_2CL_2 was added to a vigorously stirred solution of the above enol silyl ether (0.93 g, 2 mmol) in 25 mL of dry CH_2Cl_2 under N_2 at 0 °C. The colorless reaction mixture was brought to room temperature over a period of about 5 min, and the solvent was removed. The resulting yellow foam was dissolved in 10 mL of dry DMF, and 1.5 g (7.8 mmol) of powdered cesium acetate was added in one portion. The resulting heterogeneous reaction mixture was stirred at room temperature for 18 h. The reaction mixture was worked up by addition of 10 mL of water and extraction with 5 × 50 mL of ether. The combined organic fractions were dried and evaporated to furnish a yellow oil. Purification by column chromatography (5:1 hexane-ethyl acetate) furnished 0.523 g (1.3 mmol, 65% for two steps) of **7a** as a yellow oil. This product was identical in all regards with a sample prepared by reaction of the anion **2a** with acetoxyacetyl chloride by inverse addition. IR: 1750, 1740 cm^{-1}. MS: 409 (M^+, 5.3), 308 (M^+ - 101, 10), 236 (imine$^+$ - 1, 54), 43 ($C_2H_3CO^+$, 100). NMR: δ 7.4 (m, 7 H), 6.9 (m, 3 H), 6.3-6.2 (dd, 1 H, J = 8.2 Hz, J = 14.0 Hz), 5.2 (d, 1 H, J = 17.0 Hz), 5.1 (d, 1 H, J = 8.1 Hz), 4.8 (d, 1 H, J = 17.0 Hz), 3.7 (s, 3 H), 3.6 (s, 3 H), 2.1 (s, 3 H).

The Selectride reduction of **7a** gave **8a** in 50% yield as a yellow oil. IR: 3200, 1755, 1740 cm^{-1}. CI-MS: 412 (M^+ + 1, 1.8), 160 (M^+ - 252, 100). NMR: δ 7.4 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 2 H, J = 7.7 Hz, J = 16.1 Hz), 4.8 (dd, 2 H, J = 0.9 Hz, J = 7.8 Hz), 4.3 (m, 2 H), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 3 H), 2.1 (s, 3 H). Tosylation in the usual manner[11] furnished a yellow mixture. Column chromatography and pooling of the fractions with NMR spectra consistent with the desired (s near 2.3 ppm) product provided the desired product in about 70% yield. However attempts to obtain this tosylate in chromatographically homogeneous form failed, and thus **8a** could not be completely characterized.

When subjected to 2.2 equiv of CH_3ONa in a THF-CH_3OH mixture at room temperature for 2 h, **8a** provided the epoxide **9a** as a yellow semisolid in about 80% crude yield. The latter was chromatographically nonhomogeneous and thus was not completely characterized.

The conversion **9a** to **10a** involved reaction with 1.5 equiv of Superhydride in THF at 5-7 °C for 48 h. The last step proceeded in about 50% yield after column chromatography (2:1 hexane-ethyl acetate). Semisolid. IR: 3300, 1750 cm^{-1}. NMR: δ 7.3-7.1 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, J = 7.8 Hz, J = 16.0 Hz), 4.8 (dd, 1 H, J = 0.6, J = 7.8 Hz), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.64 (s, 3 H), 1.35-1.32 (d, 3 H, J = 6.4 Hz).

7c, a yellow oil, was prepared in 85% yield from **2c** by inverse addition to excess acetoxyacetyl chloride as above. IR: 1750, 1740 cm^{-1}. MS: 423 (M^+, 1.8), 322 (M^+ - 3.1), 250 (imine$^+$ - 1, 9.3), 84 (M^+ - 339, 100). NMR: δ 7.4 (m, 7 H), 6.8 (dd, 2 H, J = 2.2 Hz, J = 6.8 Hz), 6.6 (s, 1 H), 5.3 (d, 1 H, J = 7.9 Hz), 4.9 (s, 1 H), 4.8 (d, 1 H, J = 7.9 Hz), 3.7 (s, 3 H), 2.1 (s, 3 H), 1.9 (d, 3 H, J = 1.2 Hz). In converting this compound to the corresponding tosylate and the epoxide problems similar to the case of the simple cinnamyl compound were encountered. The opening of this epoxide to the secondary alcohol involved reaction with Superhydride in THF at 5-7 °C for 48 h. The reaction proceeded in about 50% yield.

10c, a semi-solid, had IR and mass spectra similar to that of the diastereoisomer A. NMR: δ 7.4-7.2 (m, 7 H), 6.8 (dd, 2 H, J = 2.0 Hz, J = 8.9 Hz), 6.4 (br s, 1 H), 4.6 (s, 1 H), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 3 H), 1.9 (s, 3 H), 1.37 (d, 3 H, J = 6.4 Hz).

(17) Corey, E. J.; Rucker, C.; Hua, D. H.; Cho, H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(18) Details of data collection and structure solution are as follows. The diffraction intensities of a 0.03 × 0.30 × 0.30 mm crystal were collected at 295 K with graphite monochromatized Mo Kα radiation using $\theta/2\theta$ scan technique with profile analysis[19] to a $2\theta_{max}$ = 45° on an Euraf Nonius CAD-4 diffractometer. A total of 1815 unique reflections were measured of which only 794 were considered significant ($I_{net} > 2.5\sigma(I_{net})$). The normal Lorentz and polarization corrections were applied, but no absorption corrections made because of the small value of μ. Cell parameters were obtained by least-square treatment of the setting angles of 15 reflections with 26.0 < 2θ < 28.0°. The structure was solved by direct methods using the NRCVAX[20] system of programs and refined by full matrix least-squares to a final residuals of R_f and R_w of 0.095 and 0.102, respectively ($R_f = \Sigma(F_v - F_c)/\Sigma(F_v)$; $R_w = \Sigma w(F_v - F_c)^2/\Sigma(wF_v)^2$). The least-squares cycle was calculated with 33 atoms, 137 parameters, and 787 reflections. The relatively high residuals are probably due to the small size and poor quality of the crystals. The final difference map showed no peaks greater than 0.37 e Å^{-3}. Because of this only the Si atom was refined anisotropically and no attempt was made to locate the H atoms. The compound has a molecular weight of 462 and belongs to monoclinic group with P_{21}; a = 6.349 (3), b = 19.936 (8), and c = 10.6967 (20) Å; β = 99.39 (5)°; V = 1335.7 Å^{-3}; ρ_c = 1.148 mg m^{-3}; $Z = 2\Lambda$ = 0.70930 Å.

(19) Gabe, E. J. *J. Appl. Crystallogr.* **1978**, *11*, 114.

(20) Gabe, E. J.; LePage, Y.; Chadland, J. P.; Lee, F. L.; White, P. S. *J. Appl. Crystallogr.* **1989**, *22*, 384.

Synthesis of Prostaglandins by Conjugate Addition and Alkylation of a Directed Enolate Ion. 4,5-Allenyl Prostaglandins[1]

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Received January 8, 1990

Over the previous two decades many elegant syntheses of prostaglandins, which in the more sophisticated forms, allow the stereospecific introduction of the various asymmetric carbons have been accomplished. However, among these approaches the cuprate addition/enolate alkylation of a suitable cyclopentenone[2] stands out because of brevity and convergence. The recent reports by Noyori[3] and Corey[4] and their colleagues have reduced to practice the conversion of 4-alkoxycyclopentenones to prostaglandin E_2 (PGE_2) by conjugate addition of an organocopper derivative of the lower side chain followed by alkylation of the resulting carbanion with methyl 7-halohept-2-enoate.[5]

(1) Contribution No. 772 from the Institute of Organic Chemistry.

(2) (a) For an early tandem alkylation, see: Patterson, J. W.; Fried, J. H. *J. Org. Chem.* **1974**, *39*, 2506. (b) For a review of tandem alkylations, see: Taylor, R. J. K. *Synthesis* **1985**, 364.

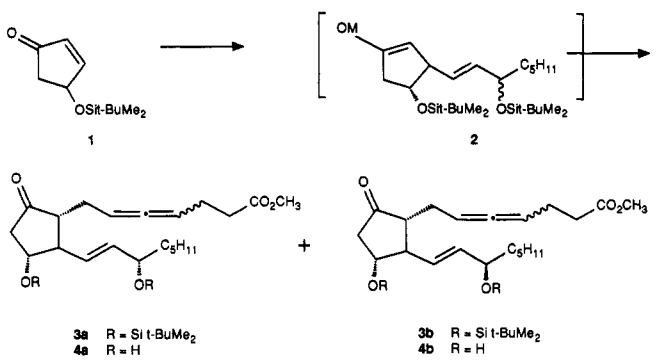
(3) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718.

(4) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.

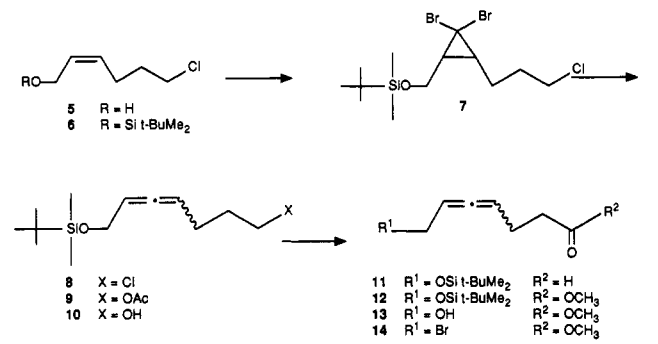
(5) For a variant on the tandem alkylation which circumvents the loss of the C-11 hydroxyl by incorporating it in a ring, see: Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 4726.

0022-3263/90/1955-5528$02.50/0

Scheme I



Scheme II



The highly convergent nature of these syntheses and the availability of optically pure precursors make tandem alkylation of cyclopentenones extremely practical. The subject of this paper is the application of the Tardella tin enolate alkylation developed by Noyori to the synthesis of 4,5-allenic prostaglandins, a pharmacologically important class of compounds.[6]

The tandem alkylation sequence for the synthesis of allenic prostaglandins is depicted in Scheme I. The requisite bromide for the enolate alkylation step was prepared as shown in Scheme II. Thus, 6-chlorohex-2-ynol,[7] readily available from propargyl alcohol and 1,3-bromochloropropane, was hydrogenated to the cis olefin[8] **5** and subsequently protected as the *tert*-butyldimethylsilyl ether[9] **6**. Phase-transfer cyclopropanation of **6** with bromoform and aqueous potassium hydroxide gave the dibromocyclopropane **7**, which on treatment with *n*-butyllithium[10] opened to the racemic allene **8**. The chloro function of **8** was transformed into a hydroxyl group via the acetate **9** and ester hydrolysis. Oxidation of alcohol **10** with dimethyl sulfoxide–oxalyl chloride[11] gave the aldehyde **11** which upon further oxidation with *m*-chloroperbenzoic acid and diazomethane esterification gave the silyl ether ester **12**. The silyl ether protecting group was removed from **12** by acetic acid hydrolysis, and the resulting alcohol **13** was converted into bromide **14** by esterification[12] with methanesulfonyl chloride followed by displacement with lithium bromide.

The reaction conditions employed for the tandem alkylation of enone **1** are those described by Noyori and colleagues[3] with the exception that a standard three-necked flask was used as a reaction vessel in place of their special apparatus. The intermediate enolate **2** was alkylated with bromide **14**, which was sufficiently reactive to give virtually complete alkylation at −22 °C in 18 h. Aqueous workup and chromatography of the reaction mixture gave a racemic and epimeric mixture of the desired 4,5-didehydro-PGE_2 derivatives **3a** and **3b** in the 28% yield. The other materials eluting from this chromatography were excess bromide **14**, tin compounds, n-Bu_3P, and nonalkylated ketone derived from **2** (less than 5%). The cause for the low overall yield of this process is destruction of the intermediate enolate **2** during the course of the alkylation step.[13] One possible explanation for this is the lower reactivity of bromide **14**. Noyori and colleagues[3] report good yields for reactive halides such as methyl 7-iodo-5-heptynoate (76%) and methyl (*Z*)-7-iodo-5-heptenoate (78%), which give reasonable conversions in 20–40 h at −30 °C. However, the less reactive methyl 7-iodoheptanoate required a −20 °C alkylation temperature and produced only 20% of PGE_1. In the present investigation bromide **14** gave reasonable rates of alkylation only near −20 °C and various attempts to convert alcohol **13** to the corresponding iodide were unsuccessful.[14] Following cleavage of the silyl ether protecting groups, the C-15 epimers were separated by chromatography to give the 15α and 15β isomers **4a** and **4b**.[6a] It was immediately apparent from the complexity of the high-field ^1H NMR spectra of these two products that each was a mixture of two diastereomers about the allene moiety. The presence of two closely spaced methyl ester signals in the NMR spectra of nearly equal intensity indicates that **4a** and **4b** are each about 1:1 mixtures, implying that there was essentially no diastereoselection in the enolate alkylation step of this tandem process. At the initiation of this study the possibility that bromide **14** would undergo S_N2' alkylation to give substituted 1,3-butadiene products was considered. There is precedent for S_N2 substitution of alkenyl bromides with enolate nucleophiles.[15] The NMR spectra of **4a** and **4b** are incompatible with a butadiene structure or possible acetylenes arising from any base-catalyzed isomerization of the allene function.

These results demonstrate that the tandem alkylation of enone **1** with a cuprate reagent followed by alkylation of the corresponding tin enolate with bromide **14** is a viable synthetic method for 4,5-didehydro-PGE_2. Because the optically active forms of **1** and the vinyl iodide precursor

(6) (a) Crabbe, P.; Carpio, H. *J. Chem. Soc., Chem. Commun.* **1972**, 904. (b) For a review of allenyl prostaglandins, see: Muchowski, J. M. *CRC Handbook of Eicosanoids: Prostaglandins and Related Lipids*; Willis, A. L., Ed.; CRC Press: Boca Raton, FL, 1987; Vol. 1, Part B, p 19.

(7) Rachlin, A. I.; Wasyliw, N.; Goldberg, M. W. *J. Org. Chem.* **1961**, *26*, 2688. These workers prepared **5** by alkylation of the THP ether of propargyl alcohol with 1,3-bromochloropropane followed by hydrolysis of the THP ether. However, **5** may be prepared directly by alkylation of the dianion of propargyl alcohol itself using 2 equiv of $LiNH_2$ in THF/NH_3 (1). For an alternate method, see: White, W. L.; Anzeveno, B. L.; Johnson, F. *J. Org. Chem.* **1982**, *47*, 2379.

(8) Holton, R. A.; Zoeller, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 2124.

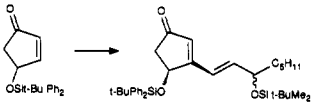
(9) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(10) (a) Doering, W. E.; La Flamme, P. M. *Tetrahedron* **1958**, 2, 75. (b) Moore, W. R.; Ward, H. R. *J. Org. Chem.* **1960**, *25*, 2073. (c) Skattebol, L. *Acta Chem. Scand.* **1963**, *17*, 1683.

(11) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(12) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

(13) In similar experiment, the conjugate addition of the same cuprate derivative of the lower side chain to enone i was quenched by aqueous workup before the alkylation procedure and found to yield 57% of cyclopentanone ii:



(14) In support of this analysis is the work of Gooding (Gooding, O. *J. Org. Chem.*, submitted) who has shown that the much more reactive trifluoromethanesulfonate of methyl 7-hydroxy-5-heptynoate gives excellent yields of alkylation product in much shorter reaction times.

(15) Lathbury, D.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1986**, 114.

of the PGE_2 lower side chain have been employed to produce a single enantiomer of PGE_2, the extension of the methodology described here to the synthesis of single enantiomers of **4a** awaits only the preparation of the separate enantiomers of allene **14**.

Experimental Section

(*Z*)-6-Chlorohex-2-en-1-ol (5). A solution of 6-chloro-2-hexyn-1-ol (52.08 g, 0.393 mol)[7] in 400 mL of ethanol was hydrogenated at atmospheric pressure in the presence of 5% $Pd/CaCO_3$ (3 g, lead poisoned, Aldrich) until a total of 8.7 L of hydrogen was absorbed. After filtration of the catalyst and evaporation of the ethanol, the resulting residue was distilled to yield 49.2 g (93%) of **5**, bp 75–85 °C (12 mm).

(*Z*)-6-Chlorohex-2-en-1-ol *tert*-Butyldimethylsilyl Ether (6). This ether was prepared by the standard procedure[9] from **5** in 92% yield: bp 85–90 °C (10 mm); IR (film) 3000, 2890, 2745, 1250, 1075 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 5.6–5.2 (m, 2 H), 4.24 (d, J = 6 Hz, 2 H), 3.52 (t, J = 6 Hz, 2 H), 2.3–2.1 (m, 2 H), 1.7–2.0 (m, 2 H), 0.90 (s, 9 H), and 0.07 (s, 6 H). Anal. Calcd for $C_{12}H_{25}ClOSi$: C, 57.91; H, 10.13. Found: C, 58.06; H, 10.16.

***dl*-2-(3-Chloropropyl)-1,1-dibromo-3-((*tert*-butyldimethylsiloxy)methyl)cyclopropane (7).** To a mixture of $HCBr_3$ (140 mL, 1.60 mol), aqueous KOH (2 mL, 50%), and n-Bu_4NBr (2 g) in a 3-L Morton flask was added in one portion olefin **6** (89.15 g, 0.358 mol). With vigorous mechanical stirring, aqueous KOH (120 g, 2.14 mol in 120 mL H_2O) was added dropwise over 3 h while the reaction temperature was maintained at 50–60 °C. The reaction was continued at 50 °C for 24 h with addition of n-Bu_4NBr (2 g, several times) when TLC (silica gel; CH_2Cl_2/hexane, 1:10) indicated the olefin had been consumed. The reaction mixture was cooled, diluted with 100 mL of water and 1 L of CH_2Cl_2, and treated with 300 g of Celite. After filtration through Celite, drying, evaporation, and filtration through silica gel (CH_2Cl_2), the organic layer produced an oil which was distilled (Kugelrohr) to give 99.4 g (66%) of **7**: bp 120–130 °C (0.04 mm); IR (film) 2940, 2840, 1475, 1255, 1090 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 3.82 (dd, J = 12, 6 Hz, 1 H), 3.55 (t, J = 6 Hz, 2 H), 3.52 (dd, J = 12, 6 Hz, 1 H), 2.1–1.5 (m, 6 H), 0.90 (s, 9 H), 0.07 (s, 6 H). Anal. Calcd for $C_{13}H_{25}Br_2ClOSi$: C, 37.11; H, 5.99. Found: C, 37.29; H, 5.89.

***dl*-7-Chloro-2,3-heptadien-1-ol *tert*-Butyldimethylsilyl Ether (8).** A solution of dibromocyclopropane **7** (99.4 g, 0.236 mol) in 400 mL of ether was cooled to −60 °C and treated with n-butyllithium (167 mL of 1.5 N in hexane, 0.25 mol) over 2 h. The reaction temperature was raised to −30 °C for 45 min, and the reaction mixture was poured into 500 mL of water. The allene **8** was isolated by extraction with ether, washing with brine, drying over K_2CO_3, and rotary evaporation. The resulting residue was distilled through a short-path apparatus to give 48.5 g (79%) of **8**, bp 85–102 °C (0.3 mm).[16]

***dl*-7-Acetoxy-2,3-heptadien-1-ol *tert*-Butyldimethylsilyl Ether (9).** To a solution of sodium iodide (40 g, 0.267 mol) in 125 mL of acetone was added chloroallene **8** (24.71 g, 0.0946 mol). The reaction mixture was refluxed for 25 h, cooled to room temperature, and then poured into 500 mL of ice and water. The mixture was extracted with ether (3 × 150 mL), and the combined extract was washed with brine, dried over K_2CO_3, and evaporated to give the intermediate iodo compound. This iodide was dissolved in 10 mL of DMF and added to a slurry of $(CH_3)_4N^+CH_3CO_2^-$ (0.15 mol, prepared by mixing 8.59 mL of CH_3CO_2H and 54.7 g of 25% methanolic $(CH_3)_4NOH$ followed by evaporation of the methanol) in 100 mL of DMF. The reaction temperature was maintained at 25 °C by cooling with a water bath. After 3 h the reaction mixture was poured into ice and water, and the acetate **9** was isolated by ether extraction as described above. The residue obtained on evaporation of the ether was chromatographed (silica gel, ether/hexane) and distilled to give 18.15 g (67%) of **9**: bp 95–100 °C (0.04 mm); IR (film) 2950, 2850, 1950, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (m, 2 H), 4.17 (d, J = 3 Hz, 1 H), 4.16 (d, J = 3 Hz, 1 H), 4.09 (t, J = 6.4 Hz, 2 H), 2.1 (m, 2 H), 2.04 (s, 3 H), 1.75 (m, 2 H), 0.90 (s, 9 H), 0.077 (s, 6 H). Anal. Calcd for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92. Found: C, 63.31; H, 9.79.

***dl*-7-Hydroxy-4,5-heptadienal *tert*-Butyldimethylsilyl Ether (11).** A solution of acetate **9** (18.15 g, 64 mmol) in 150 mL of methanol was cooled on ice and treated with K_2CO_3 (8.82 g, 64 mmol). After stirring 70 min at 0 °C the reaction mixture was poured into ice water and brine. The hydroxy ether **10** was isolated by extraction with ethyl acetate. After drying over K_2CO_3 and filtering, 0.2 mL of Et_3N was added, the solvent was evaporated in vacuo, and the resulting oil was freed of traces of methanol by drying under a stream of nitrogen.

In a separate flask, oxalyl chloride (10 mL, 115 mmol) in 250 mL of CH_2Cl_2 was cooled to −60 °C and treated with a solution of DMSO (17 mL, 250 mmol) in 10 mL of CH_2Cl_2, which was added over 10 min. The alcohol **10** above in 20 mL of CH_2Cl_2 was added over 5 min at −60 °C, and the reaction mixture stirred at −60 °C for 20 min. Et_3N (55 mL, 390 mmol) was added dropwise, and the reaction temperature allowed to warm to −30 °C. The reaction mixture was poured into ice water, and the aldehyde **11** was isolated by extraction with CH_2Cl_2. Chromatography (silica gel; ethyl acetate/hexane, 1:6) gave an oil which on distillation (Kugelrohr) gave 10.2 g (66%) of **11**: bp 105 °C (0.02 mm); IR (film) 2920, 2850, 1940, 1710, 1260, 1085 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, J = 2.5 Hz, 1 H), 5.28 (m, 2 H), 4.15 (m, 2 H), 2.56 (m, 2 H), 3.34 (m, 2 H), 0.09 (s, 9 H), 0.07 (s, 6 H); HRMS m/z calcd for $C_{13}H_{24}O_2Si$ (m^+ − t-Bu) 183.084134, found 183.0841.

***dl*-Methyl 7-Hydroxy-4,5-heptadienoate (13).** A solution of aldehyde **11** (6.00 g, 25 mmol) in 40 mL of CH_2Cl_2 was cooled on ice, and m-chloroperoxybenzoic acid (9 g, 80%, 42 mmol in 145 mL of CH_2Cl_2) was added dropwise over 40 min. After stirring for 1 h at 0 °C, the excess peracid was quenched with Me_2S (1.5 mL), and the m-chlorobenzoic acid was removed by filtration. The resulting solution was treated with excess diazomethane, quenched with acetic acid, and then washed with aqueous $NaHCO_3$ and brine. The solution was dried over K_2CO_3 and evaporated in vacuo to give the silyl ether **12**. Without purification **12** was dissolved in 40 mL of acetic acid and 10 mL of water and stirred at room temperature for 75 min. The solvents were then evaporated in vacuo, and the resulting oil was chromatographed (silica gel, ethyl acetate/hexane) and distilled to give 3.12 g (80%) of **13**: bp 67–77 °C (0.05 mm); IR (film) 3400, 2945, 2850, 1950, 1735, 1445 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.38 (m, 2 H), 4.09 (m, 2 H), 3.69 (s, 3 H), 2.47 (m, 2 H), 2.35 (m, 2 H), 2.07 (OH); HMRS m/z calcd for $C_8H_{12}O_3$ (M^+) 156.078645, found 156.0786.

***dl*-Methyl 7-Bromo-4,5-heptadienoate (14).** A solution of alcohol **13** (6.27 g, 40 mmol) in 100 mL of CH_2Cl_2 was treated with Et_3N (6.96 mL, 50 mmol) and cooled to −20 °C. Methanesulfonyl chloride (3.62 mL, 47 mmol) in 10 mL of CH_2Cl_2 was added over 10 min, and after another 10 min the reaction mixture was poured into ice water and the product was extracted with CH_2Cl_2. The extracts were washed with brine, dried over $MgSO_4$, and evaporated. The resulting mesylate was dissolved in 5 mL of acetone and added over 5 min to a mixture of LiBr (10 g, 115 mmol) in 70 mL of acetone at 0 °C. The reaction mixture was stirred 1 h at 0 °C and then poured into ice water. The bromide **14** was extracted with ethyl acetate, dried with brine and $MgSO_4$, and concentrated in vacuo to produce an oil which was distilled in a short-path apparatus to give 5.8 g (67%) of **14**: bp 70 °C (0.06 mm); IR (film) for 2940, 1960, 1730, 1440, 1220 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45 (m, 2 H), 3.91 (dd, J = 3.5, 12.2 Hz, 2 H), 3.69 (s, 3 H), 2.45 (m, 2 H), 2.35 (m, 2 H). HRMS m/z calcd for $C_8H_{11}O_2Br$ (m^+ − OCH_3) 186.97585, found 186.97588.

***dl*-4,5-Didehydro-11,15-*O*-bis(*tert*-butyldimethylsilyl)-PGE_2 Methyl Ester (3).** A solution of *dl*-(*E*)-3-(*tert*-butyldimethylsiloxy)-1-iodo-1-octene[17] (2.21 g, 6 mmol) in 8 mL of ether was cooled to −70 °C and treated with n-butyllithium (4.5 mL, 1.5 N in hexane) over 10 min. In a second flask CuI·$P(n\text{-}Bu)_3$ complex was prepared by addition of $P(n\text{-}Bu)_3$ (3.88 mL, 15.6 mmol) to a suspension of CuI (1.18 g, 6 mmol) in 10 mL of THF. This CuI complex solution was cooled to −70 °C, and the vinyllithium reagent prepared above was transferred into it via

(16) The ^1H NMR and mass spectra of this product indicated the presence of ~10% of the corresponding 7-bromo compound, which could not be removed by chromatography or distillation, consequently it was not further characterized.

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canula over 5 min, and the resulting cuprate reagent was stirred at −70 °C for 30 min. A solution of *dl*-4-(*tert*-butyldimethylsiloxy)-2-cyclopentenone (1)[18] (1.08 g, 5 mmol) in 3 mL of THF was added over 30 min. After an additional 30 min at −70 °C, HMPA (9.5 mL) in 3 mL of THF was added followed by a solution of triphenyltin chloride (1.94 g, 5 mmol) in 4 mL of THF. Following another 10-min period of stirring at −70 °C, a solution of bromide 14 (5.47 g, 25 mmol) in 2 mL of THF was added. The reaction mixture was then placed in a −22 °C bath for 18 h, after which it was poured in aqueous NH_4Cl. Extraction with ether followed by washing the organic layer with brine, drying over $MgSO_4$, and evaporation gave a product mixture. Chromatography of this mixture on silica gel, eluting with 5–12% ether/hexane mixtures, gave the desired produce 3 (0.796 g, 28%) as a mixture of diastereomers: IR (film) 2930, 2860, 1965, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.65–5.3 (m, 2 H), 5.2–5.0 (m, 2 H), 4.15–4.0 (m, 2 H), 3.69 and 3.67 (2 s, total 3 H), 2.70–2.55 (m, 2 H), 2.5–2.05 (m, 8 H), 1.5–1.4 (m, 2 H), 1.4–1.2 (m, 6 H), 0.9 (s, 21 H), 0.05 (m, 12 H); HRMS *m/z* calcd for $C_{33}H_{60}O_5Si_2$ (M^+) 592.3979, found 592.3984.

***dl*-4,5-Didehydro and *dl*-15-Epi-4,5-didehydro Prostaglandins E_2 Methyl Esters (4a and 4b).** A solution of bis-silyl ethers **3a** and **3b** (85 mg, 0.143 mmol) in 3 mL of CH_3CN at 0 °C was treated with 0.10 mL of 48% HF. The reaction mixture was stirred 1 h at room temperature and then quenched in aqueous $NaHCO_3$. Extraction with ethyl acetate, drying with $MgSO_4$ and evaporation gave a mixture of **4a** and **4b** which was separated by rotary chromatography on silica gel, eluting with ethyl acetate/hexane/methanol, 3:7:0.5. Isomer **4b** (11 mg, 21%) eluted first: IR (CCl_4) 2930, 2860, 1960, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72–5.62 (m, 1 H), 5.60–5.50 (m, 1 H), 5.18–5.10 (m, 1 H), 5.10–5.00 (m, 1 H), 4.15–4.05 (m, 2 H), 3.677 and 3.672 (2 s, total 3 H), 2.78 (d, *J* = 6.5 Hz, 1 H), 2.72 (d, *J* = 7.5 Hz, 1 H), 2.6–2.1 (m, 8 H), 1.65–1.45 (m, 2 H), 1.4–1.25 (m, 6 H), 0.89 (t, *J* = 6.6 Hz, 3 H); HRMS *m/z* calcd for $C_{21}H_{32}O_5$ (M^+) 364.2249, found 364.2254. Isomer **4a**[6a] (30 mg, 58%) eluted second: IR (CCl_4) 2930, 2860, 1960, 1735 cm^{-1}; ^1H NMR (300 Hz, $CDCl_3$) δ 5.8–5.7 (m, 1 H), 5.65–5.55 (m, 1 H), 5.18–5.10 (m, 1 H), 5.10–5.0 (m, 1 H), 4.2–4.1 (m, 2 H), 3.68–3.67 (2 s, total 3 H), 2.83–2.72 (m, 1 H), 2.65–2.50 (m, 1 H), 2.45–2.15 (m, 8 H), 1.60–1.50 (m, 2 H), 1.4–1.25 (m, 6 H), 0.90 (s, *J* = 6.6 Hz, 3 H); HRMS *m/z* calcd for $C_{21}H_{32}O_5$ (M^+) 364.2249, found 364.2257.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for **3a** + **3b**, **4a**,**b**, **11**, **13**, and **14** (12 pages). Ordering information is given on any current masthead page.

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Crown Ethers as a Mechanistic Probe. 2.[1] On the Mechanism of Acetyl Transfer between Phenolates

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Received October 16, 1989

Crown ethers exert various effects on organic reactions through complex formation with cations.[2] Upon complexation with a cation, a crown ether increases the effective radius of the cation, reducing the charge density. This would result in the decrease in the electrostatic interaction between the cation and its counteranion. When the cation is present as the countercation for an anionic reactant, complexation of the cation with a crown ether would affect the degree of electrostatic stabilization of the anionic centers of both the transition state and the ground state. Whether the overall rate is enhanced or retarded by the addition of a crown ether, therefore, may provide information on the distribution of negative charge in the transition state relative to the ground state. In the previous study, the inhibitory effects of crown ethers on the reactivity of anionic nucleophiles toward diphenyl *p*-nitrophenyl phosphate were taken to indicate the greater negative charge density in the transition state compared with the ground state.[1]

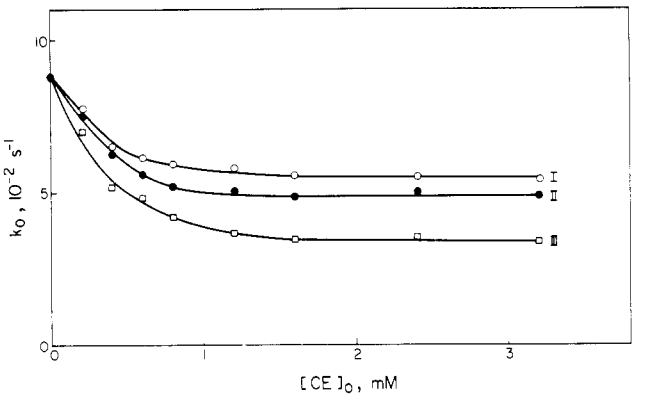
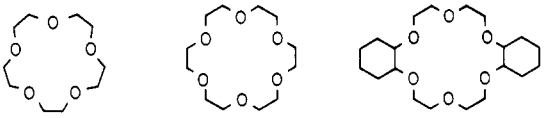


Figure 1. Dependence of k_0 on $[CE]_0$ for the release of *p*-nitrophenol by the reaction of A (1×10^{-5} M) with the sodium salt of B (8×10^{-4} M) in the presence of crown ethers I, II, and III in acetonitrile at 25 °C.

The nucleophilic displacement of carboxyl esters has been dominated by the idea of the addition–elimination mechanism involving tetrahedral intermediates.[3] Recently, however, Williams and co-workers proposed an S_N2-type concerted mechanism for the nucleophilic attack by phenolates on *p*-nitrophenyl acetate.[4] Knowledge of the distribution of negative charge in the transition state of the acetyl transfer reaction relative to that in the ground state might provide clues for the structure of the transition state. Therefore, we examined the effects of 15-crown-5 (I), 18-crown-6 (II), and dicyclohexano-18-crown-6 (III) on the rate of release of *p*-nitrophenol from the reaction of *p*-nitrophenyl acetate (A) with the sodium salt of *m*-methoxyphenolate (B) anion.



I II III

Results and Discussion

Pseudo-first-order rate constants (k_0) for the release of *p*-nitrophenol by the reaction of A (initial concentration, 1×10^{-5} M) with the sodium salt of B (initial concentration, 8×10^{-4} M)[5] were measured in the presence or absence of

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